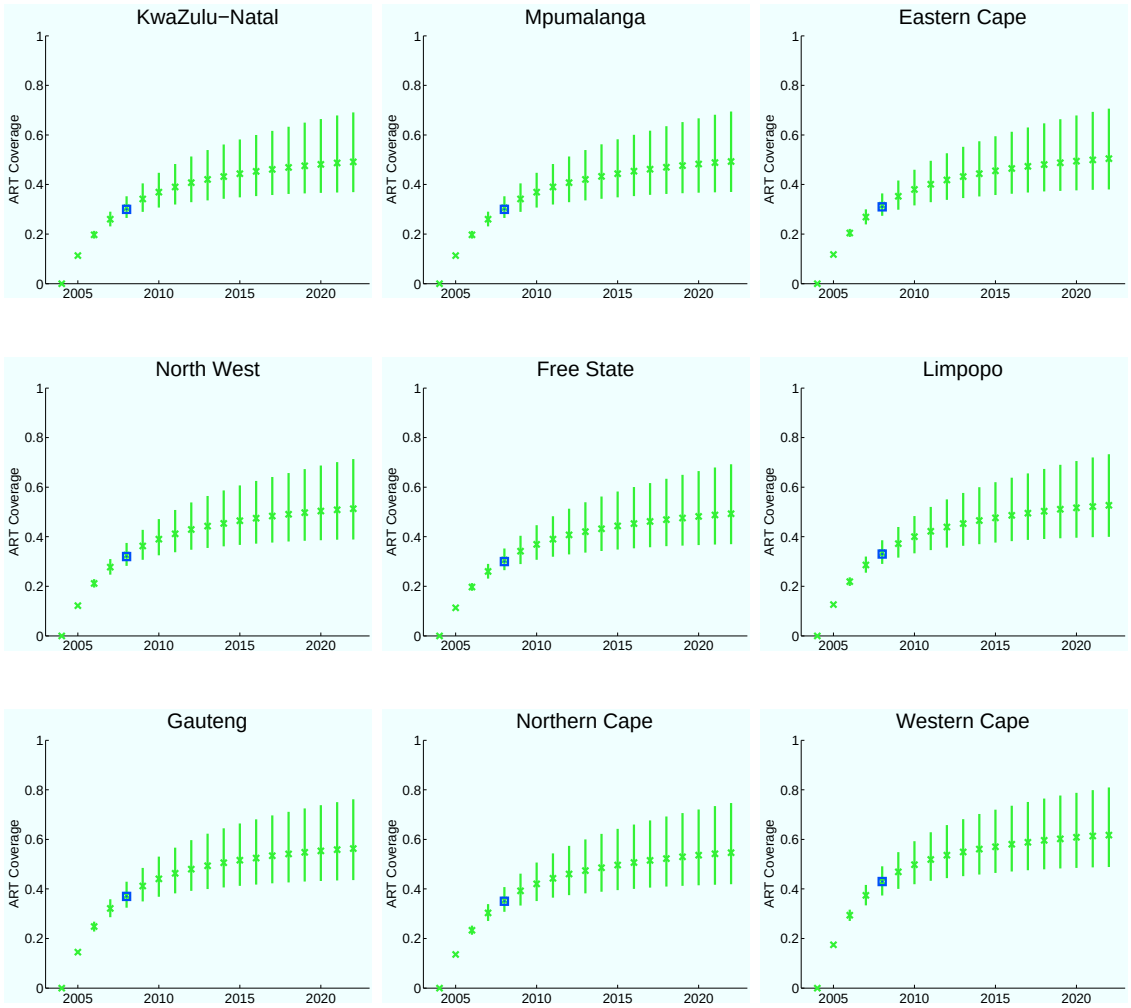
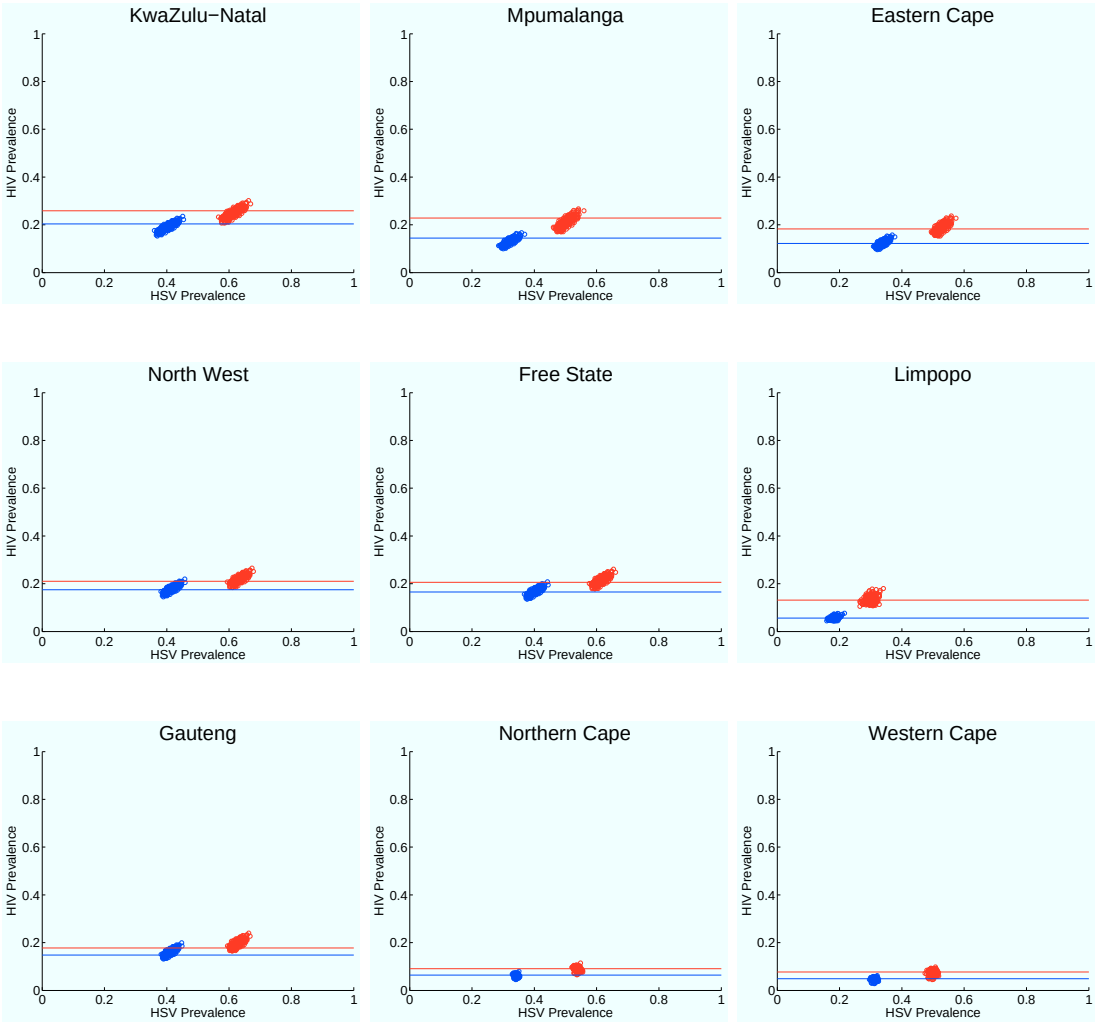
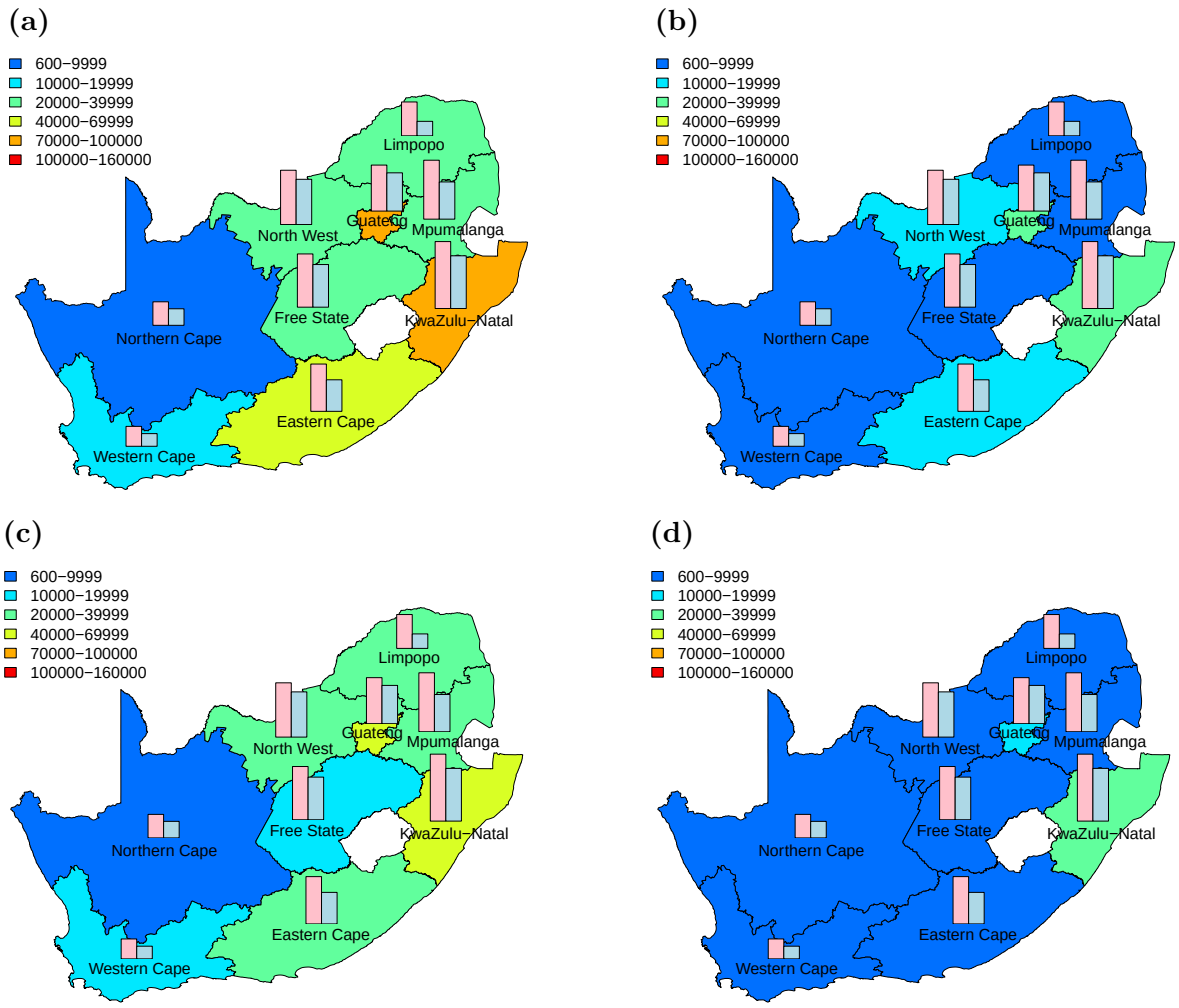
A Supplementary Figures



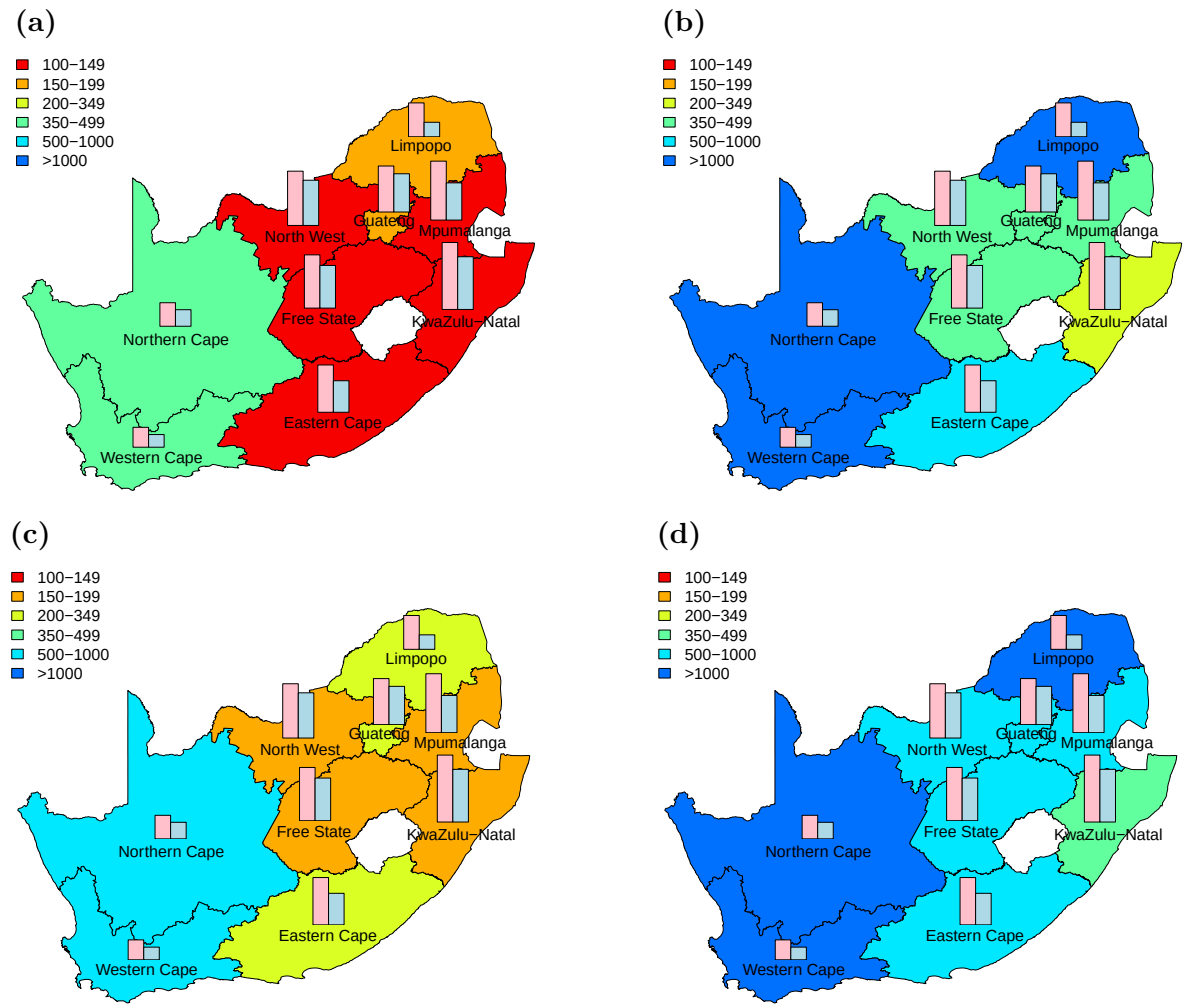
Supplementary Figure 1: Modeled ranges for the proportion of HIV-infected individuals with CD4 cell counts < 350 cells/μL on treatment in each of the 9 provinces beginning in 2004 (see Section C.1). For each year, the green line extends from the minimum to maximum coverage level; 'x' denotes median coverage level. Blue square denotes the treatment coverage level in 2008 that was estimated by the Actuarial Society of South Africa AIDS and Demographic Model [1].



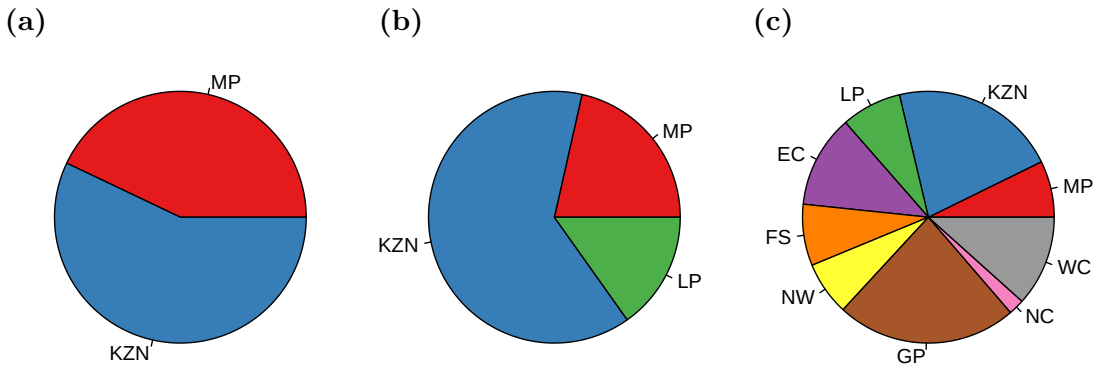
Supplementary Figure 2: Gender-specific 2004 HIV and HSV-2 equilibrium prevalence levels generated by the model after calibration (see Section C.5). Red and blue data points represent prevalence levels for women and men, respectively. Red and blue lines illustrate 2004 HIV prevalence estimates from the Actuarial Society of South Africa AIDS and Demographic Model for women and men [1], respectively.



Supplementary Figure 3: Maps of South Africa, the white area (within the country) represents the Kingdom of Lesotho. Pink and blue bars indicate the HIV prevalence in women and men, respectively, in each province at the beginning of the intervention. Province-specific estimates (median values) of the number of HIV infections prevented in either women ((a) and (c)) or men ((b) and (d)) show geographic variation in the impact of interventions. These estimates are based on the results of uncertainty analysis of the geospatial meta-population transmission model; in these analyses microbicide coverage reaches 60%. To generate (a) and (b), it was assumed the effectiveness of the microbicide in protecting against HIV infection was high (median value: 54%), to generate (c) and (d) it was assumed the effectiveness was only moderate (median value: 38%); the adherence-effectiveness relationship is based on data from the CAPRISA 004 trial [48]. In (a)-(d) the effectiveness of the microbicide in protecting against HSV-2 infection is 51% (median value) [48].

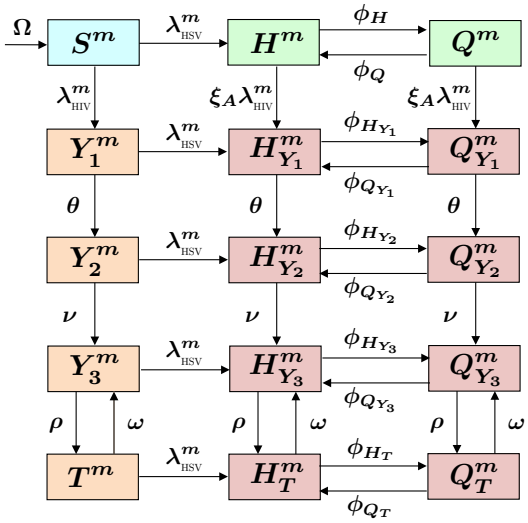


Supplementary Figure 4: Maps of South Africa, the white area (within the country) represents the Kingdom of Lesotho. Pink and blue bars indicate the HIV prevalence in women and men, respectively, in each province at the beginning of the intervention. Province-specific estimates (median values) of the number of women-years on microbicides that would be necessary to prevent one HIV infection in either women ((a) and (c)) or men ((b) and (d)) show geographic variation in the long-term efficiency of interventions. These estimates are based on the results of uncertainty analysis of the geospatial meta-population transmission model; in these analyses microbicide coverage reaches 60%. To generate (a) and (b), it was assumed the effectiveness of the microbicide in protecting against HIV infection was high (median value: 54%), to generate (c) and (d) it was assumed the effectiveness was only moderate (median value: 38%); the adherence-effectiveness relationship is based on data from the CAPRISA 004 trial [48]. In (a)-(d) the effectiveness of the microbicide in protecting against HSV-2 infection is 51% (median value) [48].

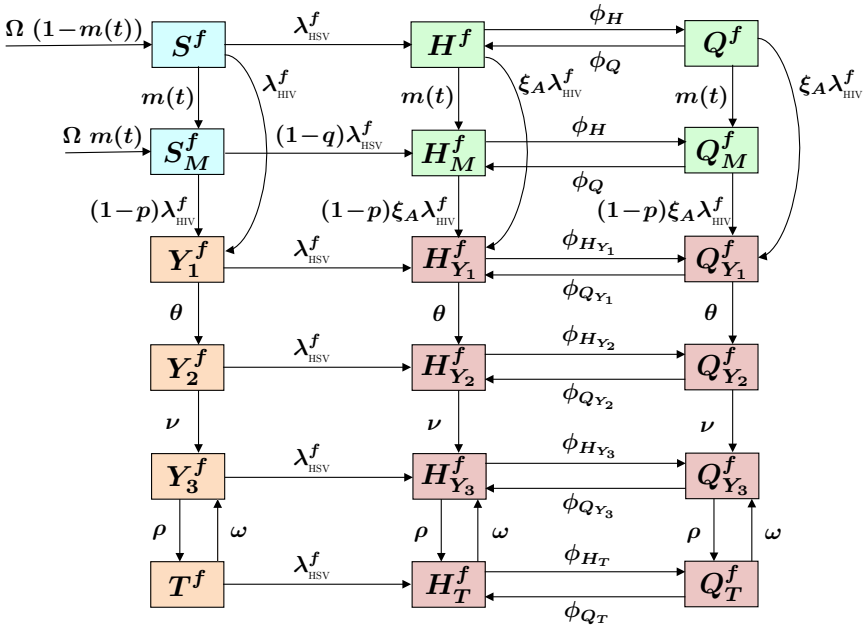


Supplementary Figure 5: The geographic resource allocation strategy (GRAS), in terms of the proportion of the supply of microbicides that would be allocated to each province in the first year of the rollout, is shown (as a pie chart) for three different rollout plans; all three are based on moderate adherence. Province abbreviations: Mpumalanga (MP), KwaZulu-Natal (KZN), Limpopo (LP), Eastern Cape (EC), Free State (FS), North West (NW), Gauteng (GP), Northern Cape (NC), and the Western Cape (WC). Charts in (a) and (b) show the GRAS that is necessary for the implementation of a utilitarian plan if: (a) 50 million microbicides are available (enough for $\approx 33\%$ of the 15-49 year old HIV-negative women in South Africa) or (b) 100 million microbicides are available (enough for $\approx 66\%$ of the 15-49 year old HIV-negative women in South Africa). The chart in (c) shows the GRAS that is necessary to implement the egalitarian rollout plan; it remains the same whether 50 or 100 million microbicides are available.

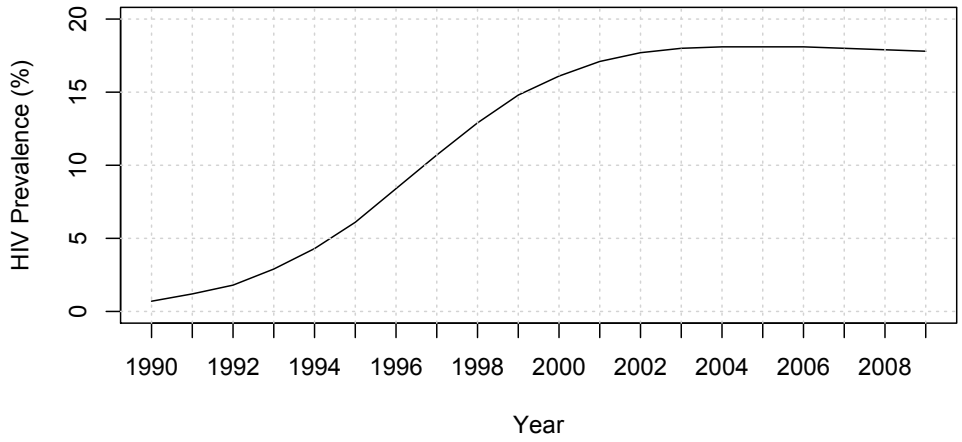
(a)



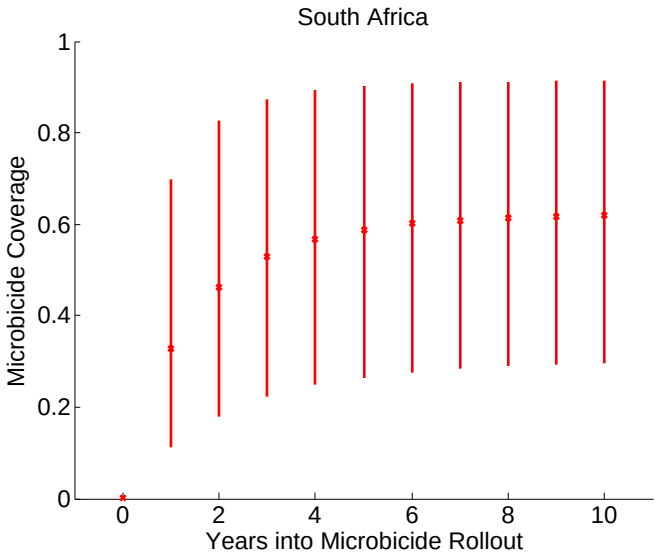
(b)



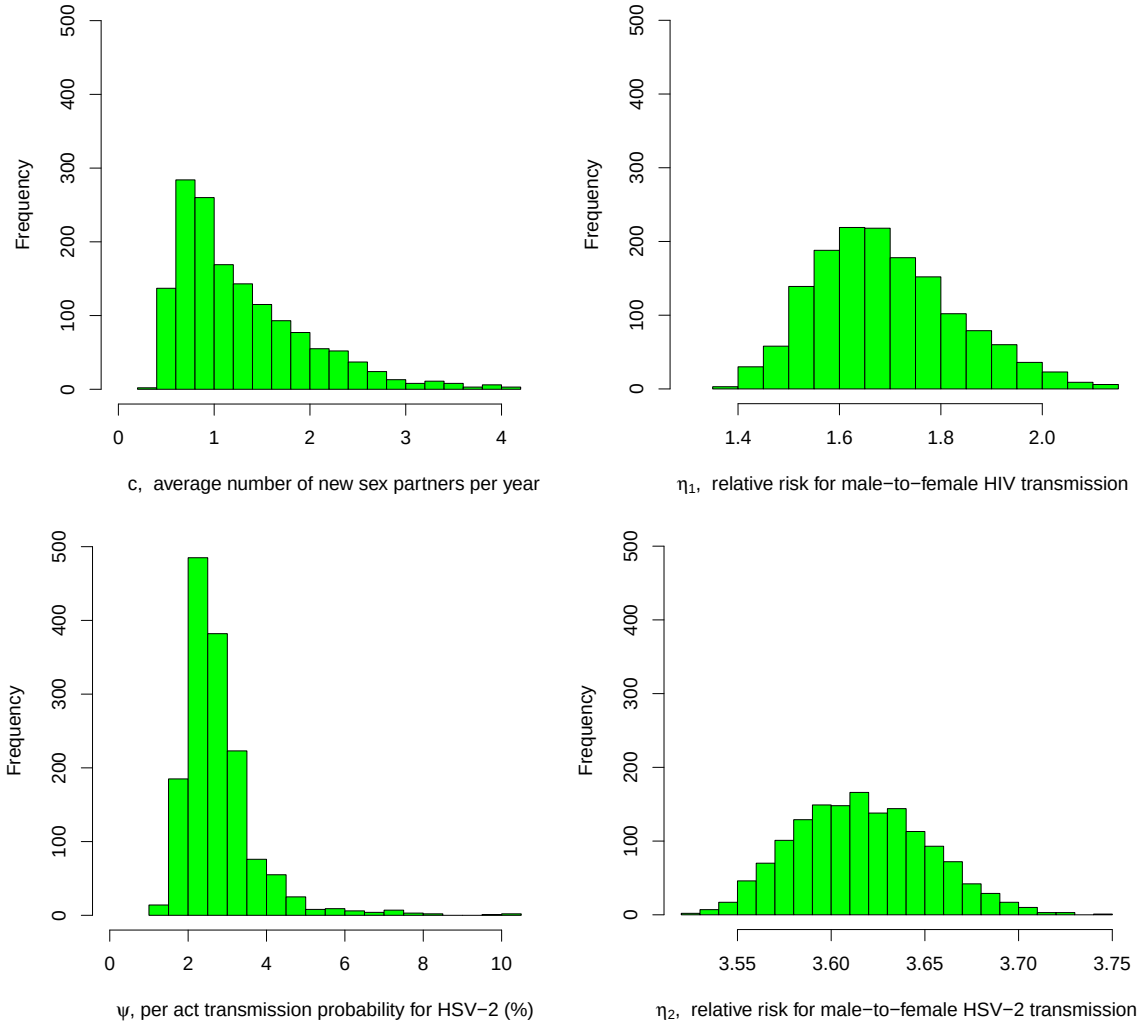
Supplementary Figure 6: Flow diagrams for the geospatial meta-population transmission model. The model structure is described in Sections C.3 and C.4. Parameter definitions are given in Supplementary Table 4. Classes representing individuals who are neither HIV nor HSV-infected are shown in light blue, only infected with HSV-2 are shown in green, only infected with HIV are shown in light orange, and coinfected with HIV and HSV-2 are shown in red. **(a)** Flow diagram for HIV/HSV-2 microbicide model for men. **(b)** Flow diagram for HIV/HSV-2 microbicide model for women.



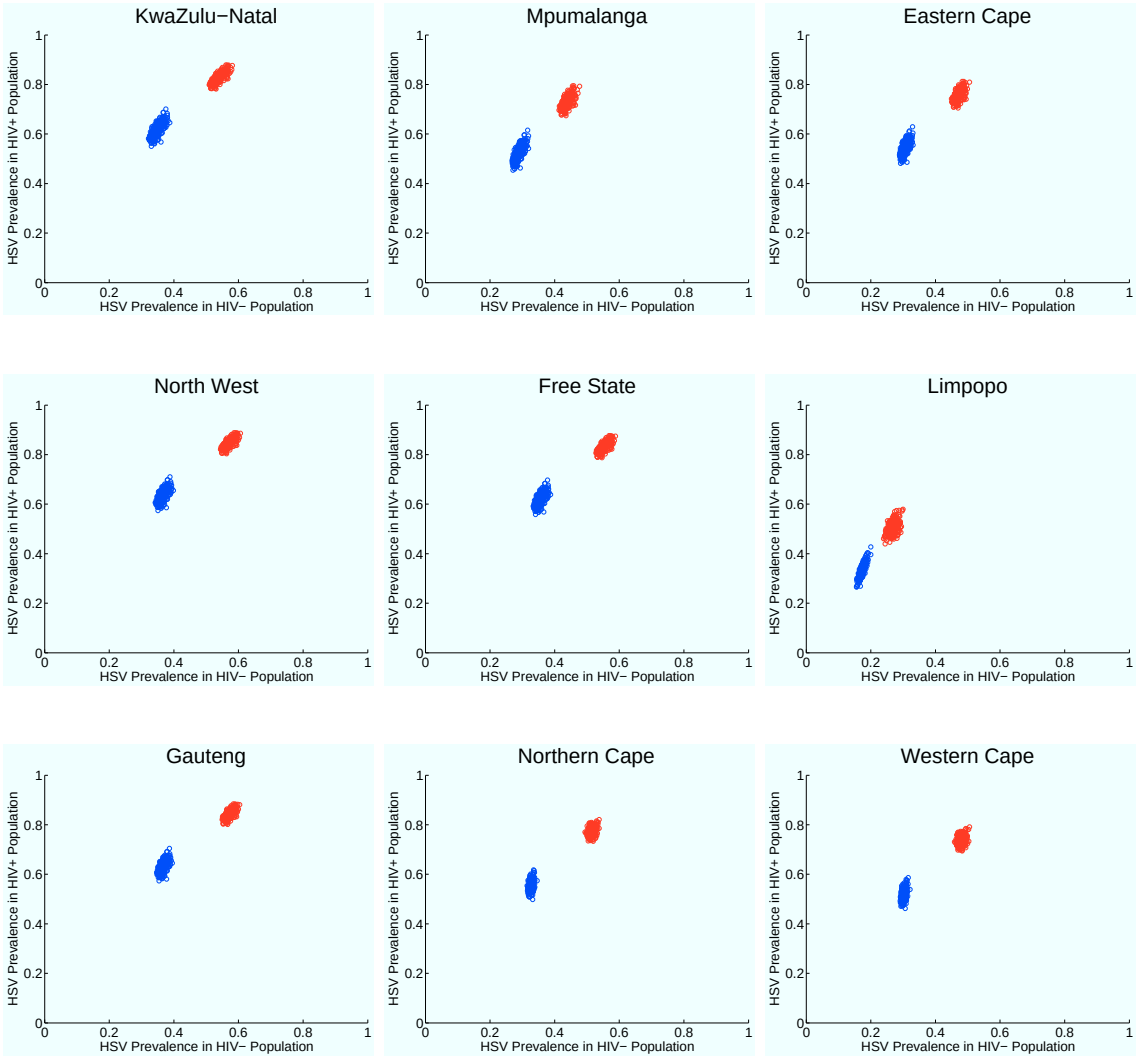
Supplementary Figure 7: HIV prevalence in South Africa (% of population ages 15-49 infected with HIV) from 1990-2009. Data from the World Bank, World Development Indicators [31].



Supplementary Figure 8: Modeled scale-up of microbicide coverage in South Africa (see Section C.2). For each year, the red line extends from the minimum to maximum coverage level; 'x' denotes median coverage level.



Supplementary Figure 9: Distributions for fitting parameters estimated by the multi-stage iterative calibration procedure described in Section C.5. Relative risks are defined per sexual partnership.



Supplementary Figure 10: Prevalence of HSV-2 in HIV-positive and HIV-negative individuals as of 2004 generated by the model after calibration (see Section C.6). Red and blue data points represent prevalence levels for women and men, respectively.

B Supplementary Tables

Supplementary Table 1: Gender-specific HIV prevalence and treatment (ART) coverage for the nine provinces of South Africa obtained from the Actuarial Society of South Africa AIDS and Demographic Model [1]. HIV prevalence levels and population sizes in 2004 were estimated from the ASSA model [1] and used for calibrating the geospatial meta-population transmission model (see Section C.5). ART coverage levels in 2008, were used to calculate province-specific annual per capita treatment rollout rates (see Section C.1).

Province	2004 HIV prevalence in women (%)	2004 HIV prevalence in men (%)	2004 Population age 15-49 (millions)	2008 ART coverage (%)
KwaZulu-Natal	26	20	5.16	30
Mpumalanga	23	14	1.79	30
Free State	21	17	1.56	30
North West	21	18	2.06	32
Guateng	18	15	5.75	37
Eastern Cape	18	12	3.28	31
Limpopo	13	6	2.76	33
Northern Cape	9	6	0.49	35
Western Cape	8	6	2.77	43

Supplementary Table 2: Model validation: Comparison of 2004 province-specific HIV incidence estimates generated by the geospatial meta-population transmission model for women and men with 2004 estimates from the Actuarial Society of South Africa AIDS and Demographic Model [1]; see Section C.7.b.

	HIV Incidence in Women (%/year)		HIV Incidence in Men (%/year)	
	median (range)	ASSA estimate	median (range)	ASSA estimate
KwaZulu-Natal	2.33 (1.68-3.36)	3.01	1.77 (1.33-2.46)	2.24
Mpumalanga	2.01 (1.45-3.01)	2.94	1.16 (0.88-1.60)	1.61
Free State	1.89 (1.35-2.73)	2.34	1.51 (1.14-2.08)	1.68
North West	1.93 (1.37-2.78)	2.48	1.62 (1.23-2.25)	1.83
Guateng	1.69 (1.19-2.43)	1.73	1.43 (1.08-1.98)	1.40
Eastern Cape	1.70 (1.21-2.52)	2.71	1.08 (0.81-1.48)	1.62
Limpopo	1.33 (0.95-2.15)	2.02	0.52 (0.39-0.76)	0.78
Northern Cape	0.71 (0.41-1.01)	1.28	0.51 (0.32-0.71)	0.80
Western Cape	0.63 (0.27-0.95)	0.99	0.41 (0.18-0.59)	0.56

Supplementary Table 3: Province-specific parameters: c denotes average number of new sex partners per year, η_1 denotes the relative risk for male-to-female HIV transmission. These two parameters are fitted parameters and are calculated from the multistage calibration procedure outlined in Section C.5. Ω denotes the recruitment rate of individuals into the sexually active population and is calculated to reflect the province-specific total population (ages 15-49) in 2004. $1-e^{-\rho}$ gives the proportion of HIV treatment-eligible individuals that go on treatment per year. IQR: interquartile range.

Province	c median (IQR)	η_1 median (IQR)	Ω median (IQR)	$1-e^{-\rho}$ value
KwaZulu-Natal	1.25 (0.90-1.85)	1.59 (1.51-1.70)	3.3×10^5 $(3.1 - 3.6 \times 10^5)$	0.122
Mpumalanga	1.02 (0.74-1.51)	2.57 (2.45-2.71)	1.1×10^5 $(1.0 - 1.2 \times 10^5)$	0.122
Free State	1.22 (0.88 1.81)	1.51 (1.43-1.61)	9.8×10^4 $(9.2 - 10.4 \times 10^4)$	0.122
North West	1.27 (0.91-1.88)	1.38 (1.31-1.47)	1.3×10^5 $(1.2 - 1.4 \times 10^5)$	0.131
Guateng	1.24 (0.89-1.83)	1.38 (1.30-1.47)	3.6×10^5 $(3.4 - 3.8 \times 10^5)$	0.156
Eastern Cape	1.04 (0.75-1.54)	2.24 (2.12-2.36)	2.0×10^5 $(1.9 - 2.1 \times 10^5)$	0.126
Limpopo	0.75 (0.54-1.12)	5.60 (5.42-5.82)	1.5×10^5 $(1.4 - 1.7 \times 10^5)$	0.136
Northern Cape	0.98 (0.71-1.45)	1.93 (1.83-2.03)	2.7×10^4 $(2.5 - 2.9 \times 10^4)$	0.146
Western Cape	0.91 (0.66-1.35)	2.36 (2.25-2.48)	1.5×10^5 $(1.4 - 1.6 \times 10^5)$	0.188

Supplementary Table 4: Parameter symbols and definitions.

Parameter Definition	Symbol
Recruitment rate into the sexually active population	Ω
Average time period for acquiring new sex partners	$1/\mu_0$
Average rate of acquiring new sex partners	c
Average number of sex acts per partnership	a
Average duration of primary HIV infection	$1/\theta$
Average time from infection with HIV to treatment eligibility (CD4<350 cells/μL)	$1/\nu$
Average survival time if HIV infected, treatment-eligible and not on treatment	$1/\mu_Y$
Per act HIV transmission probability: during primary infection	α_{Y_1}
Per act HIV transmission probability: if not yet treatment-eligible (CD4>350 cells/μL)	α_{Y_2}
Per act HIV transmission probability: if treatment-eligible (CD4<350 cells/μL)	α_{Y_3}
Per act HIV transmission probability: while on treatment	α_T
Male-to-female relative risk for acquiring HIV (per partnership)	η_1
Cofactor for increased HIV infectivity due to HSV-2 infection (per act)	ξ_I
Cofactor for increased HIV susceptibility in women due to HSV-2 infection (per partnership)	ξ_A^f
Cofactor for increased HIV susceptibility in men due to HSV-2 infection (per partnership)	ξ_A^m
Average duration of HSV-2 shedding episodes: if HIV-negative	$1/\phi_H$
Average duration of HSV-2 shedding episodes: during primary HIV infection	$1/\phi_{H_{Y_1}}$
Average duration of HSV-2 shedding episodes: if not yet treatment-eligible (CD4>350 cells/μL)	$1/\phi_{H_{Y_2}}$
Average duration of HSV-2 shedding episodes: if treatment-eligible (CD4<350 cells/μL)	$1/\phi_{H_{Y_3}}$
Average duration of HSV-2 shedding episodes: while on treatment	$1/\phi_{H_T}$
Average time between HSV-2 shedding episodes: if HIV-negative	$1/\phi_Q$
Average time between HSV-2 shedding episodes: during primary HIV infection	$1/\phi_{Q_{Y_1}}$
Average time between HSV-2 shedding episodes: if not yet treatment-eligible (CD4> 350 cells/μL)	$1/\phi_{Q_{Y_2}}$
Average time between HSV-2 shedding episodes: if treatment-eligible (CD4< 350 cells/μL)	$1/\phi_{Q_{Y_3}}$
Average time between HSV-2 shedding episodes: while on treatment	$1/\phi_{Q_T}$
Per act HSV-2 transmission probability	ψ
Male-to-female relative risk for acquiring HSV-2 (per partnership)	η_2
Proportion of treatment-eligible (CD4> 350 cells/μL) individuals beginning treatment per year	$1-e^{-\rho}$
Average survival time on treatment	$1/\mu_T$
Proportion of individuals discontinuing treatment per year	$1-e^{-\omega}$
Proportion of treated individuals with complete viral suppression	$1-\gamma_T$
Per capita microbicide uptake rate in the population	m^*
Protective effectiveness of microbicide against HIV	p
Protective effectiveness of microbicide against HSV-2	q

Supplementary Table 5: Antiretroviral therapy and microbicide parameters. Note the province-specific per capita rate of going on treatment is given in Supplementary Table 3. Complete viral suppression is defined as < 400 copies/mL [7]. The HIV effectiveness of the microbicide is influenced by adherence (see Section C.2). Per capita microbicide uptake rates, m^*, are calculated; see Section C.2. [1]Ranges of microbicide coverage and effectiveness used for sensitivity analyses. For ranges and values used in other analyses.

Parameter	Symbol	Range of values	Reference
Antiretroviral Therapy			
Average survival time on treatment	$1/\mu_T$	14-17 yrs (median 15.5)	[50]
Proportion on treatment that go off treatment per year	$1-e^{-\omega}$	$0-0.15$	[51]
Proportion on treatment that are completely virally suppressed	$1-\gamma_T$	$0.65-0.85$	[51]
Use of microbicides[1]			
Per capita microbicide uptake rate	m^*	0.03-0.38 (median 0.10)	experimental
Protective effectiveness of microbicides against HIV	p	$0.15-0.75$	[2]
Protective effectiveness of microbicides against HSV-2	q	$0.30-0.90$	[2]

Supplementary Table 6: Demographic and biological parameters. In the primary stage of HIV infection, not yet treatment-eligible (i.e., CD4 count > 350 cells/μL), treatment-eligible (i.e., CD4 count < 350 cells/μL) and on treatment, individuals are denoted Y_1, Y_2, Y_3 and T, respectively. [a]Per act transmission probabilities are calculated from viral load (see Section C.4).

Parameter	Symbol	Range of values	Reference
Demographic and Behavioral			
Average time period for acquiring new sex partners	$1/\mu_0$	$15 - 25$ years (median 20)	assumption
Average number of sex acts per partnership	a	$5 - 60$ (median 23)	[52, 53, 54, 55, 51]
Pathogenesis			
Average duration of primary HIV infection	$1/\theta$	$15 - 55$ days	[51]
Average time before becoming treatment-eligible (i.e. CD4 count > 350 cells/μL)	$1/\nu$	$5 - 7$ years	[51]
Average survival time if treatment-eligible and not on treatment (i.e. CD4 count ≤ 350 cells/μL)	$1/\mu_Y$	$3 - 7$ years	[51]
HIV Transmission			
HIV viral load in copies/mL (Y_1)		50,000-5,000,000	[8, 9]
Per act transmission probability for HIV (Y_1)	α_{Y_1}	$0.0031 - 0.0185$	calculated [a]
HIV viral load in copies/mL (Y_2)		10,000-50,000 (median 25,500)	[8, 9]
Per act transmission probability for HIV (Y_2)	α_{Y_2}	$0.0017 - 0.0031$	calculated [a]
HIV viral load in copies/mL (Y_3)		35,000-100,000 (median 63,900)	[8, 9]
Per act transmission probability for HIV (Y_3)	α_{Y_3}	$0.0027 - 0.0040$	calculated [a]
HIV viral load in copies/mL (T)		75-20,000 (median 8,000)	[8, 9]
Per act transmission probability for HIV (T)	α_T	$0.00027 - 0.0022$	calculated [a]
HSV-2 Interaction with HIV			
Cofactor for increased HIV infectivity due to HSV-2 infection (per act)	ξ_I	$1.28 - 1.72$	[3, 9, 11, 14]
Cofactor for increased HIV susceptibility in women due to HSV-2 infection (per partnership)	ξ_A^f	$1.38 - 2.39$	[15, 16, 56, 3]
Cofactor for increased HIV susceptibility in men due to HSV-2 infection (per partnership)	ξ_A^m	$1.35 - 2.35$	[15, 16, 56, 3]

Supplementary Table 7: HSV-2 parameters. Durations of viral shedding episodes reflect both clinical and subclinical HSV-2 viral shedding. The ranges for the durations of shedding episodes and the time between shedding episodes produce average annual numbers of shedding episodes between 3.7 and 4.4. [a] The per act HSV-2 transmission probability, ψ, and the relative risk for male-to-female HSV-2 transmission, η_2, are calculated via a multi-stage calibration procedure (see Section C.5) and validated against data (see Section C.7.a).

Parameter	Symbol	Range of values	Reference
Average duration of HSV-2 shedding episodes			
HIV-negative	$1/\phi_H$	$10 - 15$ days	[3]
HIV-positive			
Primary infection	$1/\phi_{H_{Y_1}}$	$15 - 20$ days	[3]
Not yet treatment-eligible (CD4 count $>$ 350 cells/μL)	$1/\phi_{H_{Y_2}}$	$15 - 20$ days	[3]
Treatment-eligible (CD4 count $<$ 350 cells/μL)	$1/\phi_{H_{Y_3}}$	$25 - 30$ days	[3]
Receiving treatment	$1/\phi_{H_T}$	$15 - 20$ days	[3]
Average time between HSV-2 shedding episodes			
HIV-negative	$1/\phi_Q$	$72 - 82$ days	[3]
HIV-positive			
Primary infection	$1/\phi_{Q_{Y_1}}$	$68 - 78$ days	[3]
Not yet treatment-eligible (CD4 count $>$ 350 cells/μL)	$1/\phi_{Q_{Y_2}}$	$68 - 78$ days	[3]
Treatment-eligible (CD4 count $<$ 350 cells/μL)	$1/\phi_{Q_{Y_3}}$	$58 - 68$ days	[3]
Receiving treatment	$1/\phi_{Q_T}$	$68 - 78$ days	[3]
HSV-2 Transmission			
Per act transmission probability for HSV-2	ψ	$0.0133 - 0.039$	fit [a]
Male-to-female relative risk for acquiring HSV-2	η_2	$3.53 - 3.74$	fit [a]

C Supplementary Methods

C.1 Modeling treatment rollout

South Africa's first national guidelines for antiretroviral therapy (ART) were introduced in 2004 with treatment rollout beginning soon after [1]. As of 2008, ART coverage (i.e. the percentage of individuals with CD4 cell counts < 350 cells/μL that are on treatment) among provinces ranged from 30-43% (see Supplementary Table 1). We model ART rollout for each province beginning in 2004.

We assume treatment-eligible individuals (i.e., those with a CD4 cell count < 350 cells/μL) begin ART at a rate $\rho(t)$ and move into the treated class, T, by setting

$$\rho(t) = \begin{cases} 0, & \text{if } t < 2004 \\ \rho, & \text{if } t \geq 2004. \end{cases} \tag{1}$$

Consequently, treatment-eligible individuals begin treatment at a per capita rate of ρ only after 2004. Three hundred simulations of the geospatial meta-population transmission model from 2004 to 2008 were conducted with per capita treatment rates ranging from 0.05 to 0.25. The per capita treatment rates were then plotted against the resulting ART coverage as of 2008. A direct relationship between the per capita treatment rate, ρ, and ART coverage achieved in 2008, which we denote C_{2008} was observed. Specifically, C_{2008} was a quadratic function of the per capita treatment rate ρ. The coefficients for this quadratic relationship were found using regression:

$$C_{2008} = -2.666\rho^2 + 2.544\rho + 0.015. \tag{2}$$

Hence, given estimates for the ART coverage achieved by 2008 in each specific province, C_{2008},

(see Supplementary Table 1), we are able to use Equation 2 to solve for the corresponding province-specific per capita treatment rates, ρ. The results of these calculations are given in Supplementary Table 3. In Supplementary Table 3, we report province-specific values of $1 - e^{-\rho}$ rather then per capita treatment rates because if individuals move to the treatment class at a per capita rate of ρ, the proportion of treatment-eligible individuals that go on treatment per year is given by $1 - e^{-\rho}$. In Supplementary Table 3, we see that this proportion ranges from 12% to 19% for the provinces in South Africa.

In Supplementary Fig. 1, the ranges for ART coverage generated by the model (i.e. the proportion of HIV-positive individuals with CD4 cell counts < 350 cells/μL on treatment) are plotted and compared with estimates from the Actuarial Society of South Africa [1]. The median ART coverage rates from the model match the coverage rates reported in 2008 almost exactly. The modeled values are shown by the green data, the ASSA estimates by the blue data. The ranges of ART coverage shown in Supplementary Fig. 1 are achieved by the point estimates of the ART treatment rate in Supplementary Table 3 due to variation in other model parameters such as HIV mortality rates and the rates of progression through disease states. When evaluating microbicides, the effect of continued treatment expansion was included in the modeling; this is shown in Supplementary Fig. 1.

C.2 Modeling microbicide rollout

We model the use of microbicides by HIV-negative women over a 10-year period. We assume that maximum coverage levels, ranging from 30% to 90%, are reached within 10 years of microbicides introduction. HIV-negative women begin using microbicide at rate $m(t)$. We model the per capita rate of microbicide adoption as time dependent with a high initial rate that diminishes

over time. Mathematically, the per capita rate is given by

$$m(t) = \begin{cases} 0, & \text{if } t < 2012 \\ m^* \left(1 + \frac{4(\text{coverage}_{\max} - \text{coverage}_t)}{\text{coverage}_{\max}}\right), & \text{if } t \geq 2012. \end{cases} \quad (3)$$

where coverage_t is the proportion of HIV-negative women on microbicide at time t and m^* is the equilibrium per capita rate of microbicide adoption. This functional form is chosen to achieve a substantial increase in adoption shortly after microbicide introduction with coverage increasing gradually to the prescribed coverage level after 10 years. Our calculated vales for m^* are given in Supplementary Table 5. The temporal dynamics of our modeled rollout of microbicides is shown in Supplementary Fig. 8.

C.3 The geospatial meta-population transmission model of coupled HIV and HSV-2 epidemics

C.3.a Model structure

We developed a geospatial meta-population transmission model to evaluate the impact of an intervention based on a vaginal microbicide that is partially effective in protecting against infection with either HIV and HSV-2. We model the transmission dynamics of HIV and HSV-2 in a heterosexual population. Specifically, our model includes the interaction between HSV-2 and HIV, in terms of both (i) increased risk of HIV acquisition for individuals infected with HSV-2 and (ii) increased HIV and HSV-2 transmission among coinfected individuals. The model includes ART, with ART coverage ramping up in conjunction with microbicide coverage (see Sections C.1 and C.2). The model is parameterized for each of the nine provinces in South Africa (see Sections C.1, C.4 and C.5) with microbicide effectiveness (HIV and HSV-2) parameterized

using data from the CAPRISA 004 clinical trial [2].

The mathematical model consists of 33 non-linear, coupled ordinary differential equations (ODEs). Each ODE tracks the flow of individuals between classes which represent gender, HIV infection status and HSV-2 infection status. The flow diagrams describing the model are shown for men in Supplementary Fig. 6a and for women in Supplementary Fig. 6b. Supplementary Table 4 summarizes the definitions of all model parameters. Classes representing individuals who are not infected with either HIV or HSV-2 are shown in light blue, only infected with HSV-2 are shown in green, only infected with HIV are shown in light orange, and coinfected with HIV and HSV-2 are shown in red. The model also tracks the stage of HIV infection, HSV-2 shedding activity or latency, HIV treatment status, and microbicide use (for women).

In the model, both men and women enter the sexually active and uninfected population (S) at a rate Ω; the total population size is denoted as N. Individuals are sexually active, in terms of acquiring new sex partners, for an average of $\frac{1}{\mu_0}$ years.

The model tracks HIV pathogenesis beginning with primary or acute infection, Y_1, characterized by high viral load and infectivity. Individuals progress from primary infection to chronic infection (Y_2) at a rate θ. As their CD4 count drops below 350 cells/μL the individual moves into the treatment-eligible, but untreated class, Y_3 at rate ν. This stage of infection is characterized by higher viral load and infectivity relative to the chronic stage; as well as by an increased removal rate, μ_Y, due to HIV-specific (and background) death rates. Individuals on ART are denoted T.

HSV-2 infected individuals may be either actively shedding virus, H, or in a latent, non-infectious state, Q. During the initial infection, individuals become infectious and actively shed virus. This is represented by moving from class S to H in Supplementary Fig. 6. The duration of shedding

episodes and the latent periods are $\frac{1}{\phi_H}$ and $\frac{1}{\phi_Q}$, respectively. Following [3], the chosen ranges for the duration and frequency of HSV-2 shedding episodes reflect the fact that HSV-2 transmission can occur even in the absence of clinical symptoms [4, 5, 6]. Hence, our shedding durations include both symptomatic and asymptomatic HSV-2 shedding.

Co-infection with HIV increases the duration of HSV-2 shedding episodes and increases the frequency of episodes [3]. This effect depends on the stage of HIV infection as well as treatment status. The main variable in the coinfected classes represents HSV-2 status while the subscript represents HIV status (e.g. Q_{Y_1} represents latently infected with HSV-2 in primary HIV infection). Superscripts denote gender (f, female and m, male) and the subscript, M, denotes women using the microbicide. N^f and N^m denote the total number of females and males, respectively.

We model the rollout and continued expansion of ART using (1) established in Section C.1. Individuals discontinue treatment at rate ω (per year). This is equivalent to a $100 * (1 - e^{-\omega})\%$ annual drop-out rate (see Supplementary Table 5). A proportion $1 - \gamma_T$ of those on ART are completely virally suppressed (i.e. < 400 viral copies/mL), and we assume are therefore noninfectious [7]. The remainder are partially virally suppressed and are therefore less infectious than untreated individuals. We model the rollout of microbicides using (3) established in Section C.2.

C.3.b Transmission probabilities for HIV

Empirical studies have shown that HIV infectivity depends strongly on the infected individual's viral load [8, 9, 10], which depends on HIV progression and treatment status. The baseline per act transmissibility (α) is calculated as a function of viral load by the empirical relationship established in [11] (see Section C.4). Increased HIV transmission due to HSV-2 infection is modeled as a multiplicative factor ξ_I for the baseline per act transmissibility α.

Empirical studies of heterosexual HIV transmission [12, 13] have shown that HIV is more transmissible from male-to-female than female-to-male due to biological differences between women and men. To reflect the biology, our model includes gender asymmetry in heterosexual transmission of HIV (i.e. HIV is more transmissible from men to women than from women to men), which we denote as the male-to-female relative risk (per partnership) for transmission of HIV η_2.

Higher HIV infectivity has been observed from individuals that are coinfected with HIV and HSV-2 compared to those infected with only HIV [9, 14] due to increased HIV viral load and/or increased access through mucosal membranes via herpetic lesions. Consequently, we model HIV-positive individuals that are also HSV-2 infected as more infectious than those that are only infected with HIV. A relationship between HSV-2 seropositivity and HIV susceptibility has been demonstrated by many epidemiological studies [15, 16, 17, 13, 18]. Possible mechanisms include that HSV-2 infection increases the likelihood of acquiring HIV by providing passage through epithelial cell layers to more vulnerable cell layers beneath and by promoting the recruitment of HIV target cells to the genital region. In our model, HIV-negative individuals that are infected with HSV-2 are more likely to become infected with HIV than those that not infected with HSV-2.

The baseline per partnership probability of HIV transmission, as determined by the status of the HIV-infected partner, is given by

$$b(\alpha, \xi_I) = 1 - (1 - \xi_I \alpha)^a \,, \tag{4}$$

where

$\alpha =$ per act transmission probability for HIV,

$\xi_I =$ cofactor (per act) for increased HIV infectivity due to HSV-2 infection,

a = average number of sex acts per partnership.

The per act transmission probability depends on the infected partner's HIV progression and can be one of $\alpha_{Y_1}, \alpha_{Y_2}, \alpha_{Y_3}$ or α_T. The cofactor for increased HIV infectivity due to HSV-2 infection, ξ_I, is only present in partnerships where the HIV-infected partner is coinfected with HSV-2. When the HIV-infected partner is not infected with HSV-2, the per partnership transmission probability is given by $b(\alpha, 1) = 1 - (1 - \alpha)^a$.

The per partnership transmission probability for HIV also reflects the status of the susceptible partner (SP), taking values of

$$\begin{aligned}
&\eta_1 b(\alpha, \xi_I), \text{ if SP is female;} \\
&\eta_1 \xi_A^f b(\alpha, \xi_I), \text{ if SP is female and infected with HSV-2;} \\
&\xi_A^m b(\alpha, \xi_I), \text{ if SP is male and infected with HSV-2;} \\
&\eta_1 (1-p) b(\alpha, \xi_I), \text{ if SP is female and using microbicides;} \\
&\eta_1 \xi_A^f (1-p) b(\alpha, \xi_I), \text{ if SP is female, infected with HSV-2 and using microbicides;}
\end{aligned} \tag{5}$$

where

η_1 = male-to-female relative risk for acquiring HIV,

ξ_A^f = cofactor (per partnership) for increased HIV susceptibility due to HSV-2 infection in women,

ξ_A^m = cofactor (per partnership) for increased HIV susceptibility due to HSV-2 infection in men,

p = protective effectiveness of the microbicide against HIV.

See Supplementary Tables 3, 5 and 6 for estimates of all parameters included in Equations (4) and (5).

C.3.c Transmission probabilities for HSV-2

HSV-2 is only transmissible during viral shedding episodes which can be clinical (i.e. genital ulcers are present) or subclinical (i.e. no ulcers or very small ulcers in unnoticeable areas) [19, 3, 20, 5, 6, 4]. Based on empirical studies, HIV influences HSV-2 transmission in our model by increasing the duration and frequency of shedding episodes in coinfected individuals [3, 21, 22, 23]. The prevalence of HSV-2 infection is higher in women than men throughout sub-Saharan Africa [24, 25] due to biological differences. To reflect this, we include gender asymmetry in the heterosexual transmission of HSV-2 (i.e. HSV-2 is more transmissible from men to women than women to men), which we denote as the male-to-female relative risk for HSV-2. The microbicide's protection against HSV-2 acquisition is also included for those women who use microbicides.

The baseline per partnership probability of HSV-2 transmission is given by

$$\sigma = 1 - (1 - \psi)^a \,, \tag{6}$$

where

$$\begin{aligned} \psi &= \text{per act transmission probability for HSV-2,} \\ a &= \text{average number of sex acts per partnership.} \end{aligned}$$

The per partnership transmission probability for HSV-2 reflects the status of the susceptible partner (SP) by taking values of

$$\begin{aligned} &\eta_2 \left[1 - (1 - \psi)^a\right], \text{ if SP is female;} \\ &\eta_2(1 - q) \left[1 - (1 - \psi)^a\right], \text{ if SP is female and using microbicides;} \end{aligned} \tag{7}$$

where

$$\eta_2 = \text{male-to-female relative risk for acquiring HSV-2,}$$

$$q = \text{protective effectiveness of the microbicide against HSV-2.}$$

See Supplementary Tables 5, 6 and 7 for estimates of all parameters included in Equations (6) and (7).

C.3.d Model equations

Supplementary Table 4 summarizes the definitions of all model parameters.

The per capita rate at which susceptible females become infected with HIV, λ^f_{HIV}, given in equation (8) depends on: HIV prevalence (P_{HIV}), HSV-2 prevalence ($P_{\text{HSV-2}}$), the average rate of acquiring new sex partners (c) and the transmission probabilities for HIV (see Section C.3.b) and HSV-2 (see Section C.3.c). Adding all possible interactions, we have that susceptible females become infected with HIV at a rate

$$\begin{aligned}\lambda^f_{\text{HIV}} = \frac{c\eta_1}{N^m}\big[&Y_1^m b(\alpha_{Y_1},1)+Y_2^m b(\alpha_{Y_2},1)+Y_3^m b(\alpha_{Y_3},1)+\gamma_T T^m b(\alpha_T,1)+(H^m_{Y_1}+Q^m_{Y_1})b(\alpha_{Y_1},\xi_I)\\ &+(H^m_{Y_2}+Q^m_{Y_2})b(\alpha_{Y_2},\xi_I)+(H^m_{Y_3}+Q^m_{Y_3})b(\alpha_{Y_3},\xi_I)+\gamma_T(H^m_T+Q^m_T)b(\alpha_T,\xi_I)\big],\end{aligned} \tag{8}$$

where $b(\alpha,\xi_I) = 1-(1-\xi_I\alpha)^a$ and $b(\alpha,1) = 1-(1-\alpha)^a$. Similarly, we have that susceptible males become infected with HIV at a rate

$$\begin{aligned}\lambda^m_{\text{HIV}} = \frac{c^m}{N^f}\Big[&Y_1^f b(\alpha_{Y_1},1)+Y_2^f b(\alpha_{Y_2},1)+Y_3^f b(\alpha_{Y_3},1)+\gamma_T T^f b(\alpha_T,1)+(H^f_{Y_1}+Q^f_{Y_1})b(\alpha_{Y_1},\xi_I)\\ &+(H^f_{Y_2}+Q^f_{Y_2})b(\alpha_{Y_2},\xi_I)+(H^f_{Y_3}+Q^f_{Y_3})b(\alpha_{Y_3},\xi_I)+\gamma_T(H^f_T+Q^f_T)b(\alpha_T,\xi_I)\Big],\end{aligned} \tag{9}$$

where $c^m = c\left(\frac{N^f}{N^m}\right)$ so that the female and male populations have the same total number of

new sex partners.

Women using microbicides acquire HIV at a rate $(1-p)\lambda^f_{\text{HIV}}$. Women that are infected with HSV-2 acquire HIV at a rate $\xi^f_A\lambda^f_{\text{HIV}}$. Women using microbicides that are infected with HSV-2 acquire HIV at a rate $\xi^f_A(1-p)\lambda^f_{\text{HIV}}$. Men that are infected with HSV-2 acquire HIV at a rate $\xi^m_A\lambda^m_{\text{HIV}}$.

For HSV-2, the per capita rates at which susceptible individuals become infected are

$$\lambda^f_{\text{HSV}} = \frac{c\eta_2}{N^m}\left(H^m + H^m_{Y_1} + H^m_{Y_2} + H^m_{Y_3} + H^m_T\right)\left[1-(1-\psi)^a\right] \tag{10}$$

and

$$\lambda^m_{\text{HSV}} = \frac{c^m}{N^f}\left(H^f + H^f_{Y_1} + H^f_{Y_2} + H^f_{Y_3} + H^f_T\right)\left[1-(1-\psi)^a\right] \tag{11}$$

for women and men, respectively. Women using microbicides acquire HSV-2 at a rate $(1-q)\lambda^f_{\text{HSV}}$.

The mathematical formulation of our model can now be specified.

$$S^{f\prime} = \frac{\Omega}{2}[1-m(t)] - \mu_0 S^f - \lambda^f_{\text{HIV}}S^f - m(t)S^f - \lambda^f_{\text{HSV}}S^f, \tag{12}$$

$$S^{f\prime}_M = \frac{\Omega}{2}m(t) - \mu_0 S^f_M - (1-p)\lambda^f_{\text{HIV}}S^f_M + m(t)S^f - (1-q)\lambda^f_{\text{HSV}}S^f_M, \tag{13}$$

$$Y^{f\prime}_1 = \lambda^f_{\text{HIV}}S^f + (1-p)\lambda^f_{\text{HIV}}S^f_M - \mu_0 Y^f_1 - \theta Y^f_1 - \lambda^f_{\text{HSV}}Y^f_1, \tag{14}$$

$$Y^{f\prime}_2 = \theta Y^f_1 - \mu_0 Y^f_2 - \nu Y^f_2 - \lambda^f_{\text{HSV}}Y^f_2, \tag{15}$$

$$Y^{f\prime}_3 = \nu Y^f_2 - \mu_Y Y^f_3 - \rho(t)Y^f_3 + \omega T^f - \lambda^f_{\text{HSV}}Y^f_3, \tag{16}$$

$$T^{f\prime} = \rho(t)Y^f_3 - \omega T^f - \mu_T T^f - \lambda^f_{\text{HSV}}T^f, \tag{17}$$

$$H^{f\prime} = -\mu_0 H^f - \xi^f_A\lambda^f_{\text{HIV}}H^f - m(t)H^f + \lambda^f_{\text{HSV}}S^f - \phi_H H^f + \phi_Q Q^f, \tag{18}$$

$$H^{f\prime}_M = -\mu_0 H^f_M - (1-p)\xi^f_A\lambda^f_{\text{HIV}}H^f_M + m(t)H^f + (1-q)\lambda^f_{\text{HSV}}S^f_M - \phi_H H^f_M + \phi_Q Q^f_M, \tag{19}$$

$$H_{Y_1}^{f\,\prime} = \xi_A^f \lambda_{\text{HIV}}^f H^f + (1-p)\xi_A^f \lambda_{\text{HIV}}^f H_M^f - \mu_0 H_{Y_1}^f - \theta H_{Y_1}^f + \lambda_{\text{HSV}}^f Y_1^f - \phi_{H_{Y_1}} H_{Y_1}^f + \phi_{Q_{Y_1}} Q_{Y_1}^f, \quad (20)$$

$$H_{Y_2}^{f\,\prime} = \theta H_{Y_1}^f - \mu_0 H_{Y_2}^f - \nu H_{Y_2}^f + \lambda_{\text{HSV}}^f Y_2^f - \phi_{H_{Y_2}} H_{Y_2}^f + \phi_{Q_{Y_2}} Q_{Y_2}^f, \quad (21)$$

$$H_{Y_3}^{f\,\prime} = \nu H_{Y_2}^f - \mu_Y H_{Y_3}^f - \rho(t) H_{Y_3}^f + \omega H_T^f + \lambda_{\text{HSV}}^f Y_3^f - \phi_{H_{Y_3}} H_{Y_3}^f + \phi_{Q_{Y_3}} Q_{Y_3}^f, \quad (22)$$

$$H_T^{f\prime} = \rho(t) H_{Y_3}^f - \omega H_T^f - \mu_T H_T^f + \lambda_{\text{HSV}}^f T^f - \phi_{H_T} H_T^f + \phi_{Q_T} Q_T^f, \quad (23)$$

$$Q^{f\prime} = -\mu_0 Q^f - \xi_A^f \lambda_{\text{HIV}}^f Q^f - m(t) Q^f + \phi_H H^f - \phi_Q Q^f, \quad (24)$$

$$Q_M^{f\,\prime} = -\mu_0 Q_M^f - (1-p)\xi_A^f \lambda_{\text{HIV}}^f Q_M^f + m(t) Q^f + \phi_H H_M^f - \phi_Q Q_M^f, \quad (25)$$

$$Q_{Y_1}^{f\,\prime} = \xi_A^f \lambda_{\text{HIV}}^f Q^f + (1-p)\xi_A^f \lambda_{\text{HIV}}^f Q_M^f - \mu_0 Q_{Y_1}^f - \theta Q_{Y_1}^f + \phi_{H_{Y_1}} H_{Y_1}^f - \phi_{Q_{Y_1}} Q_{Y_1}^f, \quad (26)$$

$$Q_{Y_2}^{f\,\prime} = \theta Q_{Y_1}^f - \mu_0 Q_{Y_2}^f - \nu Q_{Y_2}^f + \phi_{H_{Y_2}} H_{Y_2}^f - \phi_{Q_{Y_2}} Q_{Y_2}^f, \quad (27)$$

$$Q_{Y_3}^{f\,\prime} = \nu Q_{Y_2}^f - \mu_Y Q_{Y_3}^f - \rho(t) Q_{Y_3}^f + \omega Q_T^f + \phi_{H_{Y_3}} H_{Y_3}^f - \phi_{Q_{Y_3}} Q_{Y_3}^f, \quad (28)$$

$$Q_T^{f\,\prime} = \rho(t) Q_{Y_3}^f - \omega Q_T^f - \mu_T Q_T^f + \phi_{H_T} H_T^f - \phi_{Q_T} Q_T^f, \quad (29)$$

$$S^{m\prime} = \frac{\Omega}{2} - \mu_0 S^m - \lambda_{\text{HIV}}^m S^m - \lambda_{\text{HSV}}^m S^m, \quad (30)$$

$$Y_1^{m\prime} = \lambda_{\text{HIV}}^m S^m - \mu_0 Y_1^m - \theta Y_1^m - \lambda_{\text{HSV}}^m Y_1^m, \quad (31)$$

$$Y_2^{m\prime} = \theta Y_1^m - \mu_0 Y_2^m - \nu Y_2^m - \lambda_{\text{HSV}}^m Y_2^m, \quad (32)$$

$$Y_3^{m\prime} = \nu Y_2^m - \mu_Y Y_3^m - \rho(t) Y_3^m + \omega T^m - \lambda_{\text{HSV}}^m Y_3^m, \quad (33)$$

$$T^{m\prime} = \rho(t) Y_3^m - \omega T^m - \mu_T T^m - \lambda_{\text{HSV}}^m T^m, \quad (34)$$

$$H^{m\prime} = -\mu_0 H^m - \xi_A^m \lambda_{\text{HIV}}^m H^m + \lambda_{\text{HSV}}^m S^m - \phi_H H^m + \phi_Q Q^m, \quad (35)$$

$$H_{Y_1}^{m\,\prime} = \xi_A^m \lambda_{\text{HIV}}^m H^m - \mu_0 H_{Y_1}^m - \theta H_{Y_1}^m + \lambda_{\text{HSV}}^m Y_1^m - \phi_{H_{Y_1}} H_{Y_1}^m + \phi_{Q_{Y_1}} Q_{Y_1}^m, \quad (36)$$

$$H_{Y_2}^{m\,\prime} = \theta H_{Y_1}^m - \mu_0 H_{Y_2}^m - \nu H_{Y_2}^m + \lambda_{\text{HSV}}^m Y_2^m - \phi_{H_{Y_2}} H_{Y_2}^m + \phi_{Q_{Y_2}} Q_{Y_2}^m, \quad (37)$$

$$H_{Y_3}^{m\,\prime} = \nu H_{Y_2}^m - \mu_Y H_{Y_3}^m - \rho(t) H_{Y_3}^m + \omega H_T^m + \lambda_{\text{HSV}}^m Y_3^m - \phi_{H_{Y_3}} H_{Y_3}^m + \phi_{Q_{Y_3}} Q_{Y_3}^m, \quad (38)$$

$$H_T^{m\prime} = \rho(t) H_{Y_3}^m - \omega H_T^m - \mu_T H_T^m + \lambda_{\text{HSV}}^m T^m - \phi_{H_T} H_T^m + \phi_{Q_T} Q_T^m, \quad (39)$$

$$Q^{m\prime} = -\mu_0 Q^m - \xi_A^m \lambda_{\text{HIV}}^m Q^m + \phi_H H^m - \phi_Q Q^m, \tag{40}$$

$$Q_{Y_1}^{m\prime} = \xi_A^m \lambda_{\text{HIV}}^m Q^m - \mu_0 Q_{Y_1}^m - \theta Q_{Y_1}^m + \phi_{H_{Y_1}} H_{Y_1}^m - \phi_{Q_{Y_1}} Q_{Y_1}^m, \tag{41}$$

$$Q_{Y_2}^{m\prime} = \theta Q_{Y_1}^m - \mu_0 Q_{Y_2}^m - \nu Q_{Y_2}^m + \phi_{H_{Y_2}} H_{Y_2}^m - \phi_{Q_{Y_2}} Q_{Y_2}^m, \tag{42}$$

$$Q_{Y_3}^{m\prime} = \nu Q_{Y_2}^m - \mu_Y Q_{Y_3}^m - \rho(t) Q_{Y_3}^m + \omega Q_T^m + \phi_{H_{Y_3}} H_{Y_3}^m - \phi_{Q_{Y_3}} Q_{Y_3}^m, \tag{43}$$

$$Q_T^{m\prime} = \rho(t) Q_{Y_3}^m - \omega Q_T^m - \mu_T Q_T^m + \phi_{H_T} H_T^m - \phi_{Q_T} Q_T^m. \tag{44}$$

C.4 Model Parameterization

The mathematical model has a total of 34 parameters. For parameter definitions see Supplementary Table 4. Four of the parameters were estimated using a multistage calibration procedure (see Section C.5); two of these apply to all provinces (ψ, η_2) and two are province-specific (c, η_1). Parameter ranges were estimated from the literature for the remaining 30 model parameters. Twenty two of these were taken directly from the literature (see Supplementary Tables 5, 6 and 7), and the remaining eight ($\Omega, \alpha_{Y_1}, \alpha_{Y_2}, \alpha_{Y_3}, \alpha_{Y_T}, \xi_I, \xi_A^f$ and ξ_A^m) are estimated as described below.

Demography

In order to calculate Ω for each of the nine provinces, we used the fact that the total population size at equilibrium is given by

$$N^* = \frac{\Omega}{\mu_0 \left(1 - P_{HIV} \frac{\theta\nu}{\mu_Y(\mu_0+\nu+\theta)+\nu\theta}\right) + \mu_Y \left(P_{HIV} \frac{\theta\nu}{\mu_Y(\mu_0+\nu+\theta)+\nu\theta}\right)}, \tag{45}$$

where P_{HIV} is the province-specific HIV prevalence and $\frac{\theta\nu}{\mu_Y(\mu_0+\nu+\theta)}$ gives the proportion of HIV-infected individuals that are treatment-eligible (i.e., with CD4 cell counts < 350 cells/μL) and not on treatment. Using province-specific data for N^* and HIV prevalence and ranges for

θ, ν, μ_Y and μ_0 estimated from the literature [1], province-specific ranges of Ω were calculated. They are given in Supplementary Table 3.

Transmission probability for HIV (per act)

We calculated the per act transmission probabilities of HIV $\alpha_{Y_1}, \alpha_{Y_2}, \alpha_{Y_3}$ and α_T using the well-established relationship between viral load and HIV infectivity [8, 9, 10]. We use viral load data from [8, 9] and the functional formalization between HIV viral load and per act infectivity established in [11, 26] (i.e. $\alpha = 0.0018 * 2.45^{\log_{10}(\frac{\text{Viral Load}}{12500})}$) to calculate the per act transmission probabilities for each stage of HIV infection. The resulting ranges for each stage of HIV infection are given in Supplementary Table 6.

Cofactor for increased HIV infectivity due to HSV-2 infection (per act)

To calculate the cofactor for increased HIV infectivity (per act) due to HSV-2 infection, ξ_I, we used data showing that being HSV-2 seropositive increases HIV plasma viral load in both men and women [14]. A meta-analysis of Barnabas *et al.* [14] included eight studies that assessed the association between HSV-2 infection and HIV plasma viral load. Their summary estimate shows a mean increase in plasma viral load of $0.18 \log_{10}$ copies/mL (95% CI 0.01-0.34), with substantial heterogeneity among the studies. However, several of the studies included in their meta-analysis (particularly those that were restricted to men with incident or early HIV infection) did not find an association between HSV-2 infection and HIV plasma viral load. Our modeling analysis is based on the assumption that HSV-2 does increase HIV plasma viral load; therefore to guide our choice of parameter values we used the studies in the meta-analysis that showed a positive association to assume that being HSV-2 seropositive increases HIV plasma viral load by an amount ranging from $0.27 \log_{10} - 0.61 \log_{10}$ copies with a peak of $0.44 \log_{10}$ copies. Using the same relationship between viral load and the per act infection probability from [11, 26] this corresponds to a 28-72% increase in per act infectiousness (i.e. $1.28 \leq \xi_I \leq 1.72$).

Cofactor for increased HIV susceptibility due to HSV-2 infection (per partnership) To calculate the cofactor for increased HIV susceptibility due to HSV-2 infection (per partnership), ξ_A^f and ξ_A^m for women and men, respectively, we used two meta-analyses of longitudinal studies [15, 16], these analyses show that the relative risk (RR) of acquiring HIV ranges from $2.1 - 3.1$ (peak 2.7) for men and from $2.1 - 3.1$ (peak 3.1) for women. As noted in [3], HSV-2 is much more infectious than HIV, so it likely that HSV-2 transmission occurs before HIV transmission. Hence, the majority of HIV transmission to HSV-2 infected individuals would occur from a partner who is also infected with HSV-2 (i.e. coinfected). Consequently, estimates of RR from clinical trials include not only the effect of increased susceptibility (ξ_A) but are also influenced by the increased infectivity of the coinfected partners (ξ_I). Accounting for this by letting $\xi_A = \frac{RR}{b(\alpha,\xi_I)/b(\alpha,1)}$, we get ranges for the cofactor of acquiring HIV due to HSV-2 infection of 1.38-2.39 and 1.35-2.35 for women and men, respectively (i.e. $1.38 \leq \xi_A^f \leq 2.39, 1.35 \leq \xi_A^m \leq 2.35$).

Supplementary Table 4 provides a summary of all model parameter symbols and definitions. Parameter ranges are provided in Supplementary Tables 3, 5, 6 and 7. Province-specific parameters (i.e. c, η_1, Ω and ρ) are provided in Supplementary Table 3. Supplementary Table 5 gives antiretroviral therapy and microbicide parameters. Supplementary Table 6 gives HIV parameters; Supplementary Table 7 gives HSV-2 parameters.

C.5 Model Calibration

To calibrate the model to 2004 prevalence, we employed an iterative multistage procedure that first calibrates the model using country-level HIV and HSV-2 prevalence data. It then refines the calibration using province-specific HIV prevalence data [1] given in Supplementary Table 1, and produces province-specific prevalence estimates of HSV-2 prevalence. This was done because province-specific data for HIV prevalence exists, but province-specific prevalence data for HSV-2

does not exist for all provinces. We calibrated the model using four parameters for model fitting: the average number of sex partners per year (c), the male-to-female relative risk for acquiring HIV (η_1), the per act transmission probability for HSV-2 (ψ) and the male-to-female relative risk for acquiring HSV-2 (η_2).

The calibration procedure involves four stages: (1) parameter sampling, (2) calibration to gender-specific national HIV and HSV-2 prevalence, (3) calibration to province-specific HIV prevalence and (4) Monte-Carlo filtering. The calibration procedure is summarized in Algorithm 1.

Algorithm 1 Model Calibration Procedure

Stage 1. Parameter sampling
Sample model parameters using Latin Hypercube Sampling (LHS) except for c, η_1, ψ and η_2 from distributions in Supplementary Tables 3, 5, 6 and 7

Stage 2. Calibrate to gender-specific national HIV and HSV-2 prevalence
Calculate analytic expressions for disease prevalence at endemic equilibrium
For HIV equations (46), (47) and (48)
For HSV-2 equations (49), (50), (51) and (52)
Use equations (46)–(52) to calibrate c, η_1, ψ and η_2 to national HIV and HSV-2 prevalence
Expressions for c, η_1, ψ and η_2 are given by equations (53)–(56)

Stage 3. Calibrate to province-specific HIV prevalence
Make initial province-specific estimates for c and η_1 using equations (53) and (54)
Account for effect of province-specific sexual behavior, c, on HSV-2 prevalence using equations (49), (50), (51) and (52)
Account for effect of new HSV-2 prevalence on HIV using (48) and calculate new estimates for c and η_1 using equations (53) and (54)
Repeat previous steps of stage 3 until c and η_1 converge

Stage 4. Monte-Carlo Filtering

Stage 1. Parameter sampling

Using Latin Hypercube Sampling (LHS) [27, 28, 29, 30], we obtained a sample of 1500 values for each of the 30 model parameters (i.e. all parameters except c, η_1, ψ and η_2) from the distributions given in Supplementary Tables 3, 5, 6, and 7. Parameter definitions are provided in Supplementary Table 4. We used distributions of parameters rather than fixed values to conduct

uncertainty analyses.

Stage 2. Calibrate to gender-specific national HIV and HSV-2 prevalence levels

We assumed that the prevalence of both HIV and HSV-2 was at a stable endemic level when South Africa's antiretroviral treatment program was initiated in 2004. Data from the World Bank [31] shows this is a very reasonable assumption; see Supplementary Fig. 7 for HIV prevalence in South Africa from 1990-2009. We then obtained the following analytical expressions for gender-specific endemic prevalence for HIV in women $\left(P^f_{HIV}\right)$ and in men (P^m_{HIV}):

$$\begin{aligned} P^f_{HIV} = \frac{A}{c}\Big(\Big[\beta^f_{Y_1}\mu_Y(\mu_0+\nu) + \beta^f_{Y_2}\mu_Y\theta + \beta^f_{Y_3}\nu\theta\Big]\,[\mu_Y(\theta+\mu_0)(\mu_0+\nu) \\ +c\eta_1\left(\beta^m_{Y_1}\mu_Y(\mu_0+\nu) + \beta^m_{Y_2}\mu_Y\theta + \beta^m_{Y_3}\nu\theta\right)\Big]\Big)^{-1}, \end{aligned} \tag{46}$$

$$\begin{aligned} P^m_{HIV} = \frac{A}{c\eta_1}\left(\left[\beta^m_{Y_1}\mu_Y(\mu_0+\nu) + \beta^m_{Y_2}\mu_Y\theta + \beta^m_{Y_3}\nu\theta\right]\,[\mu_Y(\mu_0+\theta)(\mu_0+\nu)\right. \\ \left.+c\left(\beta^f_{Y_1}\mu_Y(\mu_0+\nu) + \beta^f_{Y_2}\mu_Y\theta + \beta^f_{Y_3}\nu\theta\right)\right]\Big)^{-1}, \end{aligned} \tag{47}$$

where

$$\begin{aligned} A = c^2\eta_1\beta^m_{Y_3}\nu^2\theta^2\beta^f_{Y_3} + \mu_Y^2(\theta^2(c^2\eta_1\beta^m_{Y_2}\beta^f_{Y_2} - (\nu+\mu_0)^2) + \theta(\mu_0+\nu)(c^2\eta_1(\beta^f_{Y_2}\beta^m_{Y_1} + \beta^m_{Y_2}\beta^f_{Y_1}) - 2\mu_0(\mu_0+\nu)) \\ + (\mu_0+\nu)^2(c^2\eta_1\beta^m_{Y_1}\beta^f_{Y_1} - \mu_0^2)) + \mu_Y\nu\theta c^2\eta_1((\beta^m_{Y_3}\beta^f_{Y_2} + \beta^m_{Y_2}\beta^f_{Y_3})\theta + (\mu_0+\nu)(\beta^m_{Y_1}\beta^f_{Y_3} + \beta^f_{Y_1}\beta^m_{Y_3})), \end{aligned}$$

and

$$\begin{aligned} \beta^f_{Y_i} &= \left[(1-P^f_{HSV})\,b(\alpha_{Y_i},1) + P^m_{HSV}\,b(\alpha_{Y_i},\xi_I)\right]\,[(1-P^m_{HSV}) + P^m_{HSV}\,\xi_A]\,, \\ \beta^m_{Y_i} &= [(1-P^m_{HSV})\,b(\alpha_{Y_i},1) + P^m_{HSV}\,b(\alpha_{Y_i},\xi_I)]\left[(1-P^f_{HSV}) + P^f_{HSV}\,\xi_A\right], \end{aligned} \tag{48}$$

and $P^f_{HSV} = 0.61$ and $P^m_{HSV} = 0.40$ are the country-level HSV-2 prevalence for women and men as of 2004, respectively [32, 24, 25]. The expressions for $\beta^f_{Y_i}$ and $\beta^m_{Y_i}$ in (48) approximate the effect of HSV-2 infection on HIV infectivity and susceptibility. For example, $\beta^f_{Y_i} = (0.39\,b(\alpha_{Y_i},1) + 0.61\,b(\alpha_{Y_i},\xi_I))(0.60 + 0.40\,\xi_A)$ reflects that 61% of HIV-infected women will be coinfected with

HSV-2 and therefore exhibit the cofactor increased HIV infectivity, ξ_I, and that 40% of HIV-negative men will be infected with HSV-2 and exhibit the cofactor increased HIV susceptibility, ξ_A.

For HSV-2, the following analytical expressions for endemic prevalence in women (P^f_{HSV}) and men (P^m_{HSV}) were obtained:

$$P^f_{HSV} = 1 - \frac{\mu^f_0(\phi^m_Q + \mu^m_0 + \phi^m_H)\left[(\phi^f_Q + \mu^f_0 + \phi^f_H)\mu^m_0 + c\sigma(\phi^f_Q + \mu^f_0)\right]}{c\sigma(\phi^f_Q + \mu^f_0)\left[(\mu^f_0 + \eta_2 c\sigma)\mu^m_0 + (\phi^m_Q + \phi^m_H)\mu^f_0 + \phi^m_Q \eta_2 c\sigma\right]}, \tag{49}$$

$$P^m_{HSV} = 1 - \frac{\mu^m_0(\phi^f_Q + \mu^f_0 + \phi^f_H)\left[(\phi^m_Q + \mu^m_0 + \phi^m_H)\mu^f_0 + \eta_2 c\sigma(\phi^m_Q + \mu^m_0)\right]}{\eta_2 c\sigma(\phi^m_Q + \mu^m_0)\left[(c\sigma + \mu^m_0)\mu^f_0 + (\phi^f_Q + \phi^f_H)\mu^m_0 + c\sigma\phi^f_Q\right]}, \tag{50}$$

where

$$\begin{aligned}
\phi^f_Q &= (1 - P^f_{HIV})\phi_Q + (P^f_{HIV}\,\hat{y_1})\phi_{Q_{Y_1}} + (P^f_{HIV}\,\hat{y_2})\phi_{Q_{Y_2}} + (P^f_{HIV}\,\hat{y_3})\phi_{Q_{Y_3}},\\
\phi^f_H &= (1 - P^f_{HIV})\phi_H + (P^f_{HIV}\,\hat{y_1})\phi_{H_{Y_1}} + (P^f_{HIV}\,\hat{y_2})\phi_{H_{Y_2}} + (P^f_{HIV}\,\hat{y_3})\phi_{H_{Y_3}},\\
\phi^m_Q &= (1 - P^m_{HIV})\phi_Q + (P^m_{HIV}\,\hat{y_1})\phi_{Q_{Y_1}} + (P^m_{HIV}\,\hat{y_2})\phi_{Q_{Y_2}} + (P^m_{HIV}\,\hat{y_3})\phi_{Q_{Y_3}},\\
\phi^m_H &= (1 - P^m_{HIV})\phi_H + (P^m_{HIV}\,\hat{y_1})\phi_{H_{Y_1}} + (P^m_{HIV}\,\hat{y_2})\phi_{H_{Y_2}} + (P^m_{HIV}\,\hat{y_3})\phi_{H_{Y_3}},\\
\mu^f_0 &= (1 - P^f_{HIV})\mu_0 + (P^f_{HIV}\,\hat{y_3})\mu_Y,\\
\mu^m_0 &= (1 - P^m_{HIV})\mu_0 + (P^m_{HIV}\,\hat{y_3})\mu_Y,
\end{aligned} \tag{51}$$

and

$$\begin{aligned}
\hat{y_1} &= \frac{\mu_Y(\mu_0 + \nu)}{\mu_Y(\mu_0 + \nu + \theta) + \nu\theta},\\
\hat{y_2} &= \frac{\theta\mu_Y}{\mu_Y(\mu_0 + \nu + \theta) + \nu\theta},\\
\hat{y_3} &= \frac{\theta\nu}{\mu_Y(\mu_0 + \nu + \theta) + \nu\theta},
\end{aligned} \tag{52}$$

and $P^f_{HIV} = 0.18$ and $P^m_{HIV} = 0.136$ are the country-level HIV prevalence for women and men as

of 2004, respectively [1]. The expressions for $\phi_Q^f, \phi_H^f, ..., \mu_0^m$ in (51) approximate the effect of HIV infection on the duration and frequency of HSV-2 shedding episodes and the overall mortality where $\hat{y_1}, \hat{y_2}$ and $\hat{y_3}$ represent the proportions of HIV-infected individuals in the primary, not yet treatment-eligible stage (i.e. individuals with CD4 cell counts > 350 cells/μL) and treatment-eligible stage (i.e. individuals with CD4 cell counts < 350 cells/μL) at the endemic equilibrium, respectively.

Using national HIV prevalence of $P_{HIV}^f = 18.0\%$ in women and $P_{HIV}^m = 13.6\%$ in men [1], and national HSV-2 prevalence of $P_{HSV}^f = 61\%$ in women and $P_{HSV}^m = 40\%$ in men [32, 24, 25], we see that Equations (46), (47), (49) and (50) become a system of 4 equations in 4 unknowns that can be solved explicitly to obtain

$$c = \frac{\mu_Y(\mu_0+\theta)(\mu_0+\nu)}{(\frac{P_{HIV}^f}{P_{HIV}^m} - P_{HIV}^f)((\theta\beta_{Y_2}^f + \beta_{Y_1}^f(\mu_0+\nu))\mu_Y + \beta_{Y_3}^f\nu\theta)}, \tag{53}$$

$$\eta_1 = \frac{\frac{P_{HIV}^f}{P_{HIV}^m}(-\frac{P_{HIV}^f}{P_{HIV}^m} + P_{HIV}^f)((\theta\beta_{Y_2}^f + \beta_{Y_1}^f(\mu_0+\nu))\mu_Y + \beta_{Y_3}^f\nu\theta)}{(P_{HIV}^f - 1)((\beta_{Y_2}^m\theta + \beta_{Y_1}^m(\mu_0+\nu))\mu_Y + \beta_{Y_3}^m\nu\theta)}, \tag{54}$$

$$\psi = 1 - \left(\frac{(c(P_{HSV}^f - \frac{P_{HSV}^f}{P_{HSV}^m}) + \mu_0^m)\phi_Q^f + (c(P_{HSV}^f - \frac{P_{HSV}^f}{P_{HSV}^m}) + \mu_0^m)\mu_0^f + \mu_0^m\phi_H^f}{c(\phi_Q^f + \mu_0^f)(P_{HSV}^f - \frac{P_{HSV}^f}{P_{HSV}^m})}\right)^{a^{-1}}, \tag{55}$$

$$\eta_2 = \frac{(\phi_Q^f + \mu_0^f)(P_{HSV}^f - \frac{P_{HSV}^f}{P_{HSV}^m})(\phi_Q^m + \mu_0^m + \phi_H^m)\frac{P_{HSV}^f}{P_{HSV}^m}\mu_0^f}{\mu_0^m(\phi_Q^m + \mu_0^m)(-1 + P_{HSV}^f)(\phi_Q^f + \mu_0^f + \phi_H^f)}. \tag{56}$$

Parameter sampling using LHS in Stage 1 established a set of 1500 values for all model parameters except c, η_1, ψ, η_2, Equations (53)-(56) were used to produce a set of 1500 values for c, η_1, ψ, η_2. The distributions obtained for these four fitting parameters are shown in Supplementary Fig. 9. We note that the average number of sex partners per year (c) and the per act transmission probability for HSV-2 (ψ) exhibit right-skewed distributions with medians of 1.16 and 2.5%, respectively. The distributions for the male-to-female relative risk for HIV transmission (η_1), and the male-to-female relative risk for HSV-2 transmission (η_2) are normal with

medians of 1.67 and 2.62, respectively.

Stage 3. Calibrate to province-specific HIV prevalence

Since province-specific HSV-2 prevalence data does not exist, we began with a baseline assumption that HSV-2 prevalence in each province is equal to the national HSV-2 prevalence (i.e. $P^f_{HSV} = 61\%, P^m_{HSV} = 40\%$) and calculated province-specific values for c and η_1 in the same way as in Stage 2 using Equations (53) and (54). Supplementary Table 1 shows the province-specific HIV prevalence data used for P^f_{HIV} and P^m_{HIV}.

As sexual behavior drives both HIV and HSV-2, the province-specific values of c calculated in the previous step will change HSV-2 prevalence within that province. We therefore recalculated HSV-2 prevalence for each province using the new province-specific estimates of c using Equations (49)-(52). Again, P^f_{HIV} and P^m_{HIV} represent province-specific HIV prevalences from Supplementary Table 1 for women and men, respectively.

As we had calculated new values for the province-specific estimates of HSV-2 prevalence, we had to update the estimates of $\beta^f_{Y_i}$ and $\beta^m_{Y_i}$ using Equation (48). This procedure reflected the effect of HSV-2 infection on (i) increasing the probability of coinfected individuals transmitting HIV and (ii) increasing the susceptibility of HSV-2 infected individuals to HIV infections. Using the updated estimates of β^f_y and β^m_y, we calculated new values for HIV prevalence for men and women in each province using Equations (47) and (46), respectively. P^f_{HSV} and P^m_{HSV} represent province-specific HSV-2 prevalence calculated for women and men, respectively. With the effect of the new HSV-2 prevalence accounted for, we proceeded to calculate new values of c and η_1 using Equations (53) and (54).

Each new set of province-specific values for c and η_1 affect province-specific HSV-2 prevalence. The new province-specific HSV-2 prevalence estimates will, in turn, affect HIV prevalence and

necessitate new values of c and η_1. Repeating this process, we set up a fixed-point iteration that quickly converged to a stable solution. Notably, the values established for HSV-2 parameters ψ and η_2 are not altered in this process. Thus, our calibration process results in province-specific values of c and η_1 as well as province-specific estimates of HSV-2 prevalence while retaining a single national-level set of values for ψ and η_2.

Stage 4: Monte-Carlo Filtering

We then filtered the resulting parameter distributions for all of the model's parameters to ensure basic feasibility requirements and refine the model's fit to empirical data. The criteria for the Monte-Carlo filtering were:

1. Individuals in the primary infection stage of HIV are more infectious than those chronically infected; infectivity increases as individuals become eligible for treatment; infectivity decreases as individuals go on treatment [7].
2. HIV prevalence in females is greater than HIV prevalence in males [1].
3. Per act HSV-2 transmission probability is less than 4% (i.e. $\psi < 0.04$) [33, 34, 3, 35].

C.6 Model Verification

In total, 1362 out of the 1500 sampled sets of parameters satisfy all three Monte-Carlo filtering criteria (i.e. only 9% of parameter sets were removed through this filtering process) showing that our calibration procedure produced parameter distributions consistent with empirical data: Conditon 3 was most restrictive, it was satisfied by 1367/1500 (91%) of the parameter sets; condition 1 was satisfied by 1495/1500 (99.7%); and condition 2 was satisfied by all parameter sets 1500/1500 (100%).

After calibration, HIV prevalence estimates generated by our model were an excellent fit to the 2004 HIV prevalence estimates of ASSA [1]. Supplementary Fig. 2 displays the gender-specific HIV and HSV-2 prevalence levels for each of the 9 provinces that result from our calibration procedure.

While province-specific HSV-2 prevalence data is not available, the CAPRISA 004 trial itself gives an indication of the HSV-2 prevalence in HIV-negative women in KwaZulu-Natal as about half of the study's participants were infected with HSV-2 at the beginning of the study [2]. After calibration, the model generated HSV-2 prevalence levels for women in KwaZulu-Natal between $50-60\%$ (red data in Supplementary Fig. 10) and fairly similar HSV-2 prevalence levels for the remaining provinces (red data in Supplementary Fig. 10). Supplementary Fig. 10 also shows the model generated HSV-2 prevalence levels for men (blue data). Our model predicts HSV-2 prevalence in men is lower than in women in every province, as is found throughout sub-Saharan Africa [24, 25].

C.7 Model Validation

We took two approaches to validate our mathematical model and calibration procedure: (i) we showed that the 4 parameter estimates determined by calibration (namely, c, η_1, ψ, η_2) are consistent with the limited empirical data for these parameters (see Section C.7.a), and (ii) we demonstrated that two epidemiological outcomes generated by the model are in agreement with empirical data from epidemiological studies (namely, prevalence of HSV-2 in HIV-infected individuals and gender-specific HIV incidence rates) (see Section C.7.b).

C.7.a Comparison of calibrated model parameters with empirical data

Sexual behavior

A review of four longitudinal studies of sexual behavior in Africa [36] estimated that women and men had between 0.82-1.09 and 1.19-1.83 new sex partners per year, respectively. Another study focusing on data from Kisumu, Kenya in the four-city study [37] estimated the overall average number of new sex partners per year to be 1.88 based on a mean number of non-spousal sex partners (excluding sex workers) per year of 1.67 and 1.23 for men and women, respectively [38]; a mean number of non-spousal sex partners (excluding sex workers) per year of 0.70 [39]; and a mean number of male client contacts with sex workers per year of 0.96 [39, 40]. Our calibration procedure determined province-specific ranges for the average number of new sex partners per year, c, for which the mathematical model produced gender-specific HIV prevalences consistent with those observed across South Africa. The ranges for c for each of the 9 provinces are given in Supplementary Table 3 and the distribution of c for all of South Africa is shown in Supplementary Fig. 9. The distribution for all of South Africa has median 1.16 (IQR 0.83–1.70) and is therefore very similar to the available data on sexual behavior.

Relative risk for male-to-female HIV transmission

A meta-analysis of heterosexual transmission risk [13] found a relative risk for male-to-female HIV transmission, η_1, of 1.81 and 1.02 in high and low income countries, respectively. Male-to-female transmission was found to be 1.9 (CI 1.1-3.3) times more effective than female-to-male transmission in [12]. In [41], the authors assert that male-to-female is twice as likely as female-to-male transmission in the absence of other sexually transmitted infections, and four times as likely if either partner has a genital ulcer. Clinical studies in Italy have found male-to-female

transmission is 2.3 (CI 1.1-4.8) times as likely [42, 43] with similar results found in California [44] and Thailand [45]. Our estimates for the relative risk for male-to-female HIV transmission, η_1, resulting from our calibration procedure are consistent with these data. Supplementary Table 3 provides the estimates from the calibration procedure for each of the 9 provinces. The distribution for all of South Africa (shown in Supplementary Fig. 6) has median 1.67 (IQR 1.59–1.78). For η_1 in Supplementary Table 3, we see the range for Limpopo, with median 5.60 (IQR 5.42–5.82), appears to be outside the range of empirical data. This is likely due the uniquely severe gender asymmetry in Limpopo where prevalence is 13% in women and only 6% in men. The reason for this degree of gender asymmetry in Limpopo is unknown and could be due to a variety of factors.

Relative risk for male-to-female HSV-2 transmission

Clinical trials regarding HSV-2 transmission have found an HSV-2 acquisition relative risk ratio for females versus males, η_2, of 5.1 with 95% confidence interval (CI) of 2.1–14.4 [33]. A clinical trial of valacyclovir showed male-to-female HSV-2 transmission to be 2.75 and 4.11 times more likely then female-to-male transmission in the treatment and control arms, respectively [21].

Our calibration produced a range for the male-to-female relative risk for HSV-2, η_2 (see Supplementary Table 7), with a median of 3.62 and IQR of 3.59–3.64 (see Supplementary Fig. 9 for the distribution). The range is very consistent with the available empirical data on gender asymmetry in HSV-2 transmission. Notably, the range of values for η_2 is not province-specific due to the unavailability of province-level HSV-2 prevalence data.

Per act transmission probability of HSV-2

Estimates for the per act transmission probability for HSV-2, ψ, have varied widely; from $0.05-2.2\%$ [3, 33, 34]. Our calibration procedure produced a range of values (see Supplementary Table 7) for ψ with a median of 2.5% and an IQR of $2.2-2.9\%$ (see Supplementary Fig. 9 for the distribution). This range of values extends slightly higher than the estimates from clinical trials reported in [33, 34].

C.7.b Comparison of model outputs with empirical data

Prevalence of HSV-2 in HIV-infected individuals

Available data on the prevalence of HSV-2 in HIV-infected individuals include estimates of: 79% of female and 59% of male HIV-infected blood donors in the South African National Blood Service [46]; and 82% and 86% of ART-naive HIV-infected females and males, respectively, in rural northeastern South Africa [47].

Supplementary Fig. 10 shows the gender-specific prevalence of HSV-2 infection in the HIV-positive and HIV-negative populations that the model generates after calibration. While variation among provinces does exist, we see the prevalence of HSV-2 infection in HIV-negative women to be 70-90% and 50-70% in men. This is in general agreement with the available data.

Province-specific HIV incidence

Supplementary Table 2 shows the gender-specific HIV incidence that the model generates after calibration along with estimates from the Actuarial Society of South Africa AIDS and Demographic Model [1]. Our mathematical model is calibrated to HIV and HSV-2 prevalence only, and not to incidence. Therefore, a comparison of incidence estimates generated by the model with data are a measure of the validity of the model. Our incidence estimates are comparable to those from [1] (see Supplementary Table 2) given the difficulty involved in precisely measuring incidence. When compared with the observed incidence in CAPRISA 004 of 9.1% [2], our estimates seem quite low. However, the CAPRISA 004 trial recruited high risk women [48], whereas our modeling generates incidence estimates for the general population within each province aged 15-49 years old.

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